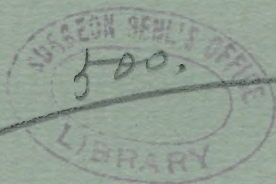


FLEXNER (S.)

A PECULIAR GLIOMA (NEUROEPITHELIOMA?) OF
THE RETINA.

By SIMON FLEXNER, M. D., *Fellow in Pathology.*

(*From the Pathological Laboratory of the Johns Hopkins University
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The patient, E. W., from whom the eye under consideration was removed was four months old. Five weeks before the date of enucleation it was noticed that something was wrong with the eye. At the time of the first examination the oculist found the pupil dilated, the anterior chamber shallow and the tension +.

The cornea was of a gray color, and presented an appearance as if about to break down. As the child was brought into the presence of the oculist the reflex often noticed in retinal glioma was observed.

So far as could be learned there is no history of malignant tumor in the ancestors of the child. The father drank to excess at one time, and suffered from amblyopia in consequence. This is the only record of disease of the eye in the ancestors of the patient.

Several years previous to the time this case occurred the eye of another child in the family, this one 6 months of age, was enucleated for a tumor which recurred and resulted in the death of the child.

Two years after the case just related still another child in the family, this one 4 months old, had a tumor of the eye for which the parents refused to have anything done. The disease soon invaded the brain causing, it is said, the skull to become twice the normal size before death occurred.

Two weeks after the enucleation of the eye under examination the remaining eye became the seat of a similar tumor, and for this the parents refused to submit to an operation. The child now passed from under the oculist's observation and its fate is unknown.



I am indebted to Dr. William Cheatham of Louisville, Ky., for the specimen and history, and I take this opportunity to acknowledge my obligations to him.

The entire eye was sent for examination preserved in alcohol, into which fluid it had been placed after its removal. On section of the eye the vitreous chamber was seen to be filled almost entirely with a tumor mass which was apparently attached to the retina.

The tumor measured 13 mm. in its longest axis and was 9 mm wide, its shape being irregularly globular. Surrounding the tumor incompletely was a small quantity of vitreous humor coagulated by the alcohol, and it is estimated that the entire extent of the vitreous chamber, not occupied by the tumor mass, was 5 mm. The retina was detached, displaced and distorted.

The tumor presented on section, after hardening, an appearance of dots and lines having a grayish-white color, which were surrounded by and imbedded in a darker and more homogeneous material. The lines appeared to issue from the retinal side of the tumor and to proceed towards its free end, which closely approached, although it did not quite reach the lens. The lines seemed to have a definite direction, and to run with little or no branching until nearly the periphery of the tumor was reached. At this place the branching was seen to be much more marked. and the tumor assumed a somewhat convoluted aspect.

When examined microscopically the tumor is seen to originate in the external portion of the retina. Although it is connected with the retina throughout a considerable part of its extent it is seen to originate at a point of microscopical size situated in the external nuclear layer. This point of origin is clearly made out, owing to the peculiar constitution of the tumor, and is represented in Fig. 1, *b*. As the tumor is followed from this point to the free edge of the retina it widens out considerably, and is seen to be attached to the internal limiting membrane for a distance of 7 mm. or thereabouts. The ora serrata is not involved in the attachment.

The external nuclear layer of the retina, on either side of the origin of the tumor, shows a striking abnormality in its structure. About midway of its thickness and for a depth of several cells is a line in which the cells stain differently from the remainder of the layer. The cells of the external nuclear layer stain readily in nuclear dyes as a rule, and such is the case in this specimen,

with the exception of the line of cells just mentioned. These cells stain very faintly in nuclear dyes, and whereas the normal cells show a quite solid body these have a finely granulated structure.

In following the tumor from its attachment to the internal limiting membrane inwards, it is evident that the connective tissue uniting the tumor with the internal limiting membrane is continuous at intervals with large and irregular areas of slight staining cells situated in this part of the tumor (Fig. 1.)

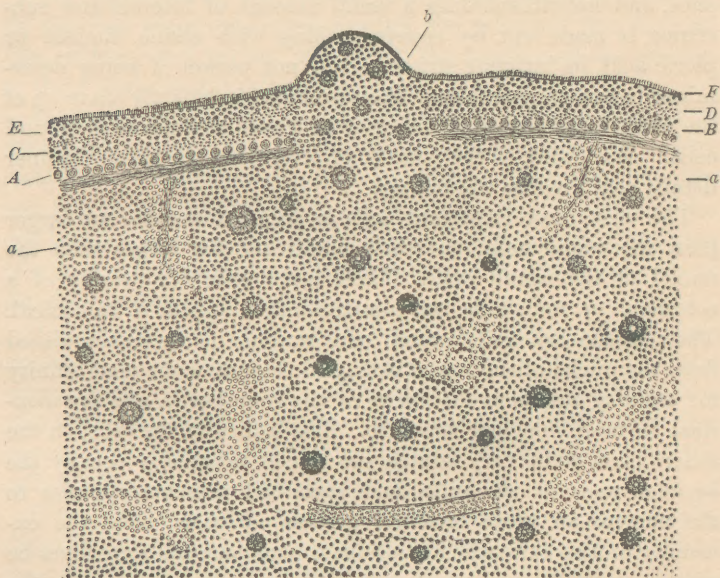


FIG. 1.

The cells composing the tumor proper may be said to consist of two principal kinds, although several kinds of cells will be described. And as the kinds of cells do not vary in the different parts of the tumor, but their particular arrangement does, it will be well to first describe the typical cells and then speak of the manner of their disposition.

The cells seen in predominating number are probably not the entire cells, but are described as such for the sake of brevity. They present the appearance of sharply stained nuclei, with scanty, often indistinct, even apparently absent cell bodies, the contours of which appear irregular, and in favorable places, as at the edges of the sections, or in very thin, partly broken parts,

thin fibre-like processes can sometimes be traced a short distance from the cell bodies. These bodies often appear as small round cells, and they will be frequently spoken of as such in this article, but we think that they have a more complicated shape and structure than this designation would imply.

These nuclei stain in the usual nuclear dyes—hæmatoxylin, carmine, magenta, iodine-green, etc., the anilines staining them more sharply than the others. They present a quite solid appearance, and notwithstanding a small amount of intercellular substance is made out by counterstaining with eosine, fuchsin or picric acid, its intimate structure did not permit of being determined in our preparations. Most probably it is partly made up of the fibre-like processes, which may be traced at times to the round cells. But owing to the manner of preserving the tissue the finer details could not be worked out.

The next most important cells in point of number are larger than the round cells, but their nuclei are not larger than the nuclei of the round cells. These large cells are usually of a columnar or rod shape, but sometimes they appear to be conical. Their nuclei are quite round, of a size not to be distinguished from the nuclei of the round cells, and they show the same affinity for staining agents as the nuclei of the round cells, and are identical in morphological structure. The bodies of the cells, on the other hand, stain very faintly, the nuclei invariably occupy the broader ends of the cells, and each cell presents opposite to the nucleus an acute terminal process. Finally, from the extremity of the cells which contains the nucleus can sometimes be seen a stalk-like prolongation which passes down between the round cells and perhaps becomes united with them, for these processes resemble those mentioned above as attached to the round cells.

Besides these there are isolated masses of cells in the tumor having a staining capacity distinct from those just mentioned. Yet, in the peculiar masses about to be described there are, mingled with the cells composing them, occasional cells, either singly or in small groups, which have the same form and staining capacity as those first described.

These peculiar cell masses exhibit the same indifference to staining agents as those observed in the external nuclear layer of the retina. Not only do they show this weak affinity for stains in general, but they present the same finely granular appearance and indistinctness as the latter.

Finally there are present in comparatively small number larger cells whose distribution is singularly irregular. These cells, which are especially to be seen in the isolated masses of light staining cells, are of variable size, and either have a perfectly homogeneous appearance without trace of nuclei, or contain blood pigment. And yet a very few cells having a coarsely granular structure, and suggesting the Mast-zellen of Ehrlich are present.

The disposition of the various cells of the tumor is important. In the first place the arrangement of the columnar cells is peculiar, striking and typical throughout the tumor, and the relation to them of the round cells is significant.

It may be stated that the columnar cells arrange themselves uniformly in one way, although an exception to this rule will be stated later. This arrangement is in the form of circles or rosettes, and it is accomplished through the juxtaposition of the sides of the cell bodies, the acute ends of the cells pointing towards the centre of the circle, while the periphery is formed by the broad ends of the cells containing the nuclei.

The rosettes vary in size, depending on the number of cells concerned in their formation, and where the acute ends of the cells are in apposition, and just before their termination a very fine although distinct membranous ring is formed, and projecting beyond this ring the delicate processes of the protoplasm of the cells forming their acute ends may be observed.

The rosettes have central lumina, the size of which also depends on the number of cells composing the circles, and they vary from almost *nil* to a considerable size. In the larger lumina, and indeed in some of the smaller, as well, a colloid or hyaline material is often seen to be present. This material is irregularly globular in shape, and a similar substance is to be seen lying in contact with the membranous ring occasionally. Indeed, it is possible to see a transformation of the delicate processes projecting beyond the ring into this material in some cases, and in these rosettes the acute processes of the cells are notably deficient.

In the rod and cone layer of the retina in this case, in parts in which the rods and cones are still visible, a similar material to that found within the lumina of the rosettes is present, and it apparently results from a gradual transformation of the rod and cone structures. For it is possible to see it in various stages of formation, and where the peculiar material is most abundant the rods and cones are either entirely absent or vestiges of them only remain.

In a few instances the peculiar round cells of the tumor were seen to occupy the lumina of certain rosettes in a way to practically exclude accidental presence.

The round cells which predominate in number over the columnar cells surround the rosettes at all places except where the rosettes are in immediate contact on one side with blood vessels as is occasionally the case. But the round cells are intimately associated with the columnar cells throughout, and the rosettes are separated from one another by the round cells. Besides the columnar cells forming the peculiar circles, a few are seen to be free among the round cells, but such single columnar cells are very rare.

It is not possible to state the exact relation of the round to the columnar cells in number, yet it may be well to remark that rosettes are quite numerous, and every field of the microscope will show a considerable number.

The cells forming the tumor, while bearing the stated relations to each other, are not disposed in one way throughout the tumor mass. At the point of the retinal attachment, and for a short distance beyond this, the cells are arranged in such a manner as to lend a quite uniform appearance to the tumor. The cells are of the two principal kinds, and are distributed everywhere alike save a few irregular masses of imperfectly staining cells corresponding to the indifferently staining cells referred to above. Where, on the other hand, the tumor is followed towards its free margin, the proper cells of the tumor take on an entirely different arrangement. With the exception of the part of the tumor adjacent to the retinal attachment, the cells are continued in the form of processes, in which there is usually a central vessel containing blood, and the thickness of the processes is made up principally of the round cells and rosettes.

This portion of the tumor is quite typical in structure. It represents the development of the tumor cells around blood vessels. It also corresponds to the lines and dots made out with the unaided eye, and it is evident that where the section passes through the length of such a process, a line is visible to the naked eye, and where it cuts one transversely a dot is seen.

The blood vessels often show thickened walls, as has previously been pointed out by Bochart (*"Untersuchungen über das Netzhaut-Gliom."* Dissert. Königsberg, 1888, p. 6). In Bochart's case the coats of the vessels were infiltrated with tumor cells, a fact not true of this case.

The processes of the tumor are separated from each other by interposed masses of cells, which behave differently with staining agents than the cells of the processes. These masses of cells not only differ from the cells comprising the processes around blood vessels, but they also differ among themselves.

In the main they remind one of the peculiar qualities of the lightly staining areas in the external nuclear layer, and the more uniform portion of the tumor near the retinal attachment. But in this portion of the tumor it is possible to see all grades of difference in staining capacity, and hence in appearance between the two kinds of tumor structure. Areas are seen in which the stain taken by the nuclei and cell bodies is just perceptibly less than in the perfectly stained places, and where the cells are just beginning to lose their outline; and this is to be followed gradually into the areas in which the cells have a very faint staining capacity, and show a finely granular protoplasm. But this is not the final stage, for isolated masses of cells are seen in which a distinct cell fusion appears to be going on even to the obliteration of the individual cell outlines.

It is not always possible to decide just what cells make up these masses when the completely altered areas are examined. But when those that are least altered are first studied, it will be seen that they consist essentially of the same elements as the unaltered ones, and even in those which have changed most remnants of the peculiar structure of the undegenerated portions may be made out. An occasional rosette is still visible and remains of blood vessels are to be seen.

Besides, in the degenerated areas there is in all cases a certain number of cells which have not undergone this change. These cells are identical with the round cells of the tumor, and they lie either singly or in small groups in the altered masses. Again, in the cell processes, otherwise perfectly stained, there is to be seen in a few instances little islands of cells which have lost their staining capacity, and which presents the peculiar characteristics of the larger unstained cell masses.

It is common to find blood in these areas. This blood is not in vessels but in the tissue, and the red corpuscles only can be made out with certainty. Blood pigment is also seen and is usually contained within cells. Reference has just been made to a process of cell fusion which is seen to be taking place extensively in some of the unstained areas. It is probable that the

large homogeneous cells represent this process on a smaller scale. And finally many cells in these masses are in a condition of fragmentation, this being especially true of the blood corpuscles.

Hence, these areas of unstained cell masses separate the processes of deeply staining cells around blood vessels one from another (Fig. 2). And the difference in the appearances of the two portions of the tumors, that is, at the retinal attachment, and the more peripheral portion is largely the result of the extent to

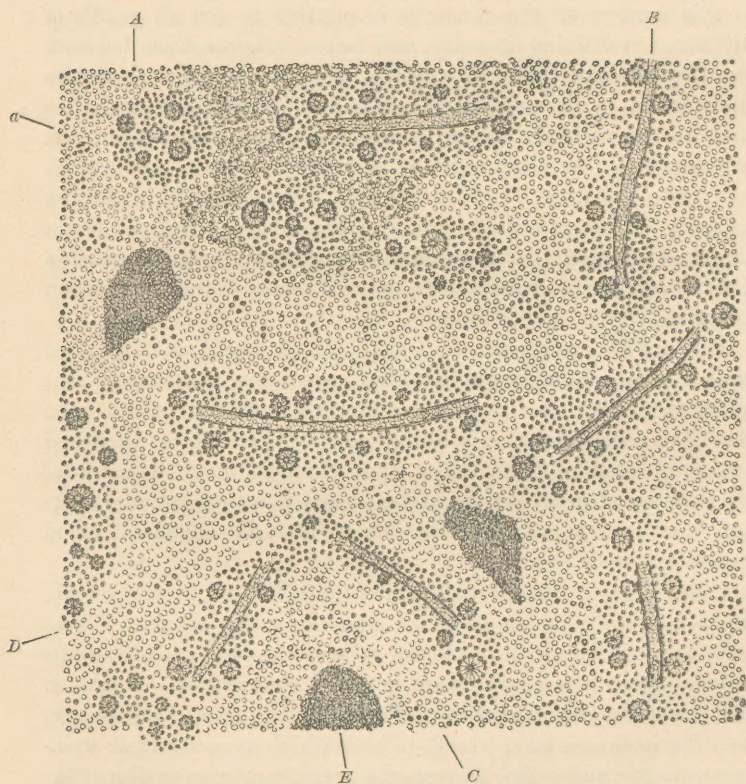


FIG. 2.

which these areas are present in either part. In the neighborhood of the attachment to the retina there are very few such areas, and those present are small, consequently the tumor at this place looks quite solid and uniform. On the other hand, the peripheral portion shows large areas of unstained cells, the cell processes are strongly contrasted, and the peculiar character of this portion of the tumor results.

But this alone cannot completely explain the difference in aspect between the two portions of the tumor; for not only do the same number and extent of degenerated areas not exist in the two parts, but the blood vessels are not present in the same number or relations. In the attached portion of the tumor but few vessels are present, while they are numerous as the lens is approached.

The degeneration of a part of the tumor cells has been described in other cases of retinal glioma,¹ and indeed is not uncommon. And not only are the cells removed from the vessels the subject of such alteration, but those in immediate contact with the vessels, and in our case remains of vessels are visible in the degenerated areas.

The tumor is almost purely cellular. A very few small bands of connective tissue are to be seen, and these are limited principally to the attached portion of the tumor. There was a deposit of lime salts in the degenerated portions.

From the foregoing it is evident that the tumor is to be regarded as having been originally uniform, and that the present appearance is to be explained by the degeneration of larger or smaller masses of cells. And it is to be borne in mind that a degeneration of cells similar to that seen in the various portions of the tumor is present in the external nuclear layer of the retina, from which layer the tumor takes its origin.

The consideration that glioma may have its starting point in the external nuclear layer of the retina, although affirmed by Knapp, Schweigger, Rindfleisch, Von Recklinghausen and others has been opposed by some histologists, and especially by Iwanoff (*Arch. f. Ophth.*, 1884, Bd. 15, p. 69).

The objections urged by Iwanoff are founded on the origin of the term "glioma," for, as he states, it was introduced by Virchow to indicate a tumor having neuroglia for its basis, and so becomes a misnomer when applied to one having a more highly organized tissue for its foundation. And he urges further, that if the view of the development of the retina as taught by M. Schultze is accepted, it is necessary to regard the two most external layers of the retina, that is, the external nuclear layer and rod and cone layer, as nervous in origin. And, hence, besides the term "glioma" being out of place as applied to a structure derived from such elements, he has grave doubts of the possibility of the proliferation of them at all.

¹ Bochart, *Idem.*, p. 10.

As to this last position it seems to us that it is probably going too far to deny the possibility of a proliferation of the elements of these structures. For in our case there cannot be the least doubt as to the place of origin of the tumor, that it was in the external nuclear layer, and that far from invading other layers of the retina it has not spread out in this one to any extent.

But there are other reasons for regarding this tumor as originating in the external layers of the retina. Attention has already been directed to the peculiar fact that a similar cell degeneration, to that so largely present in the tumor, is seen in the external nuclear layer; and when the cells composing the greater part of the tumor, that is, the apparently round cells, are compared with those of the external nuclear layer they will be seen to have the

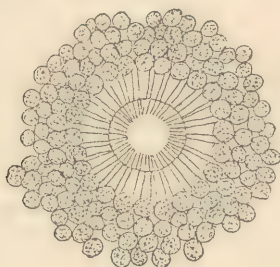


FIG. 3.

same form, size and staining affinity. Hence, on morphological grounds there is much evidence of similarity existing between the round cells of the tumor and the cells of the external nuclear layer, and when the columnar cells are examined more closely a more interesting fact becomes apparent.

It will be recalled that in the description given of the rosettes it was expressly stated that the nuclei of the cells composing them were not to be distinguished from the nuclei of the round cells, that just before the termination of the cells forming the rosettes a membranous ring was formed, and that projecting beyond this ring could often be seen fine protoplasmic processes of the cells, and further, that the nuclei of the cells always occupied the opposite and larger ends of the cells. Then surrounding these cells and in close contact with them were the round cells of the tumor.

If morphologically it is impossible to distinguish between the round cells of the tumor and the cells of the external nuclear layer of the retina, so do we consider that in each of the numerous

rosettes can be seen the rod and cone layer of the retina reproduced in miniature. For it is possible to see in the membranous ring the external limiting membrane of the retina, beyond it, projecting into the lumen of the rosettes, the delicate processes of protoplasm corresponding to the rods and cones, and opposite to these the nuclei to which these processes are united. And then surrounding these nuclei, which form a part of the external nuclear layer, as it were, are the numerous round cells of the tumor which are indistinguishable from the cells of the external nuclear layer. Finally, there are to be made out, here and there, processes proceeding from the bases of the columnar cells. So that it is to be regarded that the external nuclear layer of the retina, together with the layer of rods and cones, do not show a structure materially different from that of the tumor; the sensory epithelium of the retina, with its complex arrangement, not being distinguishable from the arrangement of the cells of the tumor.

But it is not to be considered that in every rosette the matured rods and cone layer of the retina is reproduced. While this is the case in some of them others show a structure suggesting the embryonic type. In certain rosettes the processes are quite wanting, again they are present in a rudimentary form, consisting of knob-like projections, and finally they can be recognized as distinct prolongations of the kind described. A process similar to this gradual change is seen in the embryo in those animals, in which the development of the rods and cones is incomplete at birth, and it is described by Hertwig (*"Lehrbuch der Entwicklungsgeschichte des Menschen und der Wirbelthiere,"* 1888, pp. 357 and 358) as follows: "In all vertebrates, so long as the rods and cones are not present, the inner layer of the optic cup is separated from the outer by a complete smooth contour proceeding outwards from the *membrana externa*. Later there appears upon this membrane numerous small, refractive knob-like processes that have been produced from the peripheral ends of the external nuclear or visual cells. These knobs consist of a protoplasmic material that stains in carmine, they extend somewhat lengthwise and form the internal segments of the rods and cones. Finally there appears on their surface the external segments, the lamellated structure of which led Max Schultze and W. Müller to compare them to cuticularizations."

Hence, this tumor is regarded as one in which the two most external layers of the retina have been reproduced, that the reproduction has taken place partly around blood vessels, that many of the tumor structures have degenerated, and the original appearance of the tumor has been much modified by this degeneration.

Is it proper to speak of this tumor as glioma? We think not. Firstly, as Iwanoff states the term was introduced to mean a tumor having its origin in neuroglia, and this tumor certainly does not have such an origin. But how then is it necessary to consider his second reason, that of the nervous structure of the two most external layers of the retina? Embryology has now shown us that these structures are not to be considered as purely nervous. It is believed (Balfour and Foster, "Elements of Embryology," 1883, p. 145; Schwalbe, "Lehrbuch der Anatomie der Sinnesorgane," 1887, p. 93) that in the course of development the retina becomes divided into an outer part corresponding to the epithelial lining of the cerebro-spinal canal, yielding what may be called the visual cells (Sehzellen, W. Müller) of the eye, *i. e.*, the cells forming the outer nuclear layer, and the layer of rods and cones attached to them, and an inner part consisting of the remaining layers of the retina, including the nerve fibres, which correspond morphologically to the substance of the brain and spinal cord. Kölliker (Entwicklungsgeschichte des Menschen und der höheren Thiere, 1879, Vol. II, p. 693) regards the rods and cones as cuticularizations of the cells destined to form the external nuclear layer, while Schwalbe (*idem.*, pp. 92 and 93) states that the retina can be divided into two parts consisting of the cerebral portion of W. Müller (Gehirnschicht of Schwalbe) and the epithelial layer. This latter Schwalbe denominates neuro-epithelium, and it comprises the layer of external nuclei, the external limiting membrane and the layer of rods and cones, and finds its analogue in the epithelial cells of taste and of smell. Finally Schäfer ("Elements of Histology," 1885, p. 222) calls the elements the sensory or neural epithelium of the retina.

Hence, while we agree with Iwanoff that in view of the origin of the term "glioma," and in consideration of its significance, it is a misnomer to include under it tumors which spring from tissue other than neuroglia, it is clear that it cannot now, on embryological grounds, be urged that because of the peculiar nature of these structures their proliferation is hardly possible. For according to the view accepted at the present time, the layers of the retina

from which our tumor has taken its origin, is epithelial and not purely nervous in origin. Again, tumors having the highly organized tissue of the central nervous system for their foundation have been reported by Klebs ("Die Allgemeine Pathologie," 1889, p. 790).

In view of these facts, and inasmuch as record of a tumor similar to this one has not come to our notice, we propose for tumors arising from one or both of the epithelial layers of the retina the name of "neuro-epithelioma." In offering this name, and indeed in adopting the explanation which we have for the tumor under consideration, we are not unmindful of the fact that, perhaps, a closer study based on other cases under more favorable circumstances may lead to clearer views of the origin of such tumors, and hence to a more rational classification. But with the knowledge at our command at this time such a conclusion as we have arrived at is certainly not without warrant.

Aside from the interest which attaches to this tumor on account of its peculiarity of structure, we think it is quite as interesting when considered in the light of the embryonic origin of tumors in general. According to this doctrine, first propounded by Cohnheim: "In the early stage of embryonic development more cells are produced than are required for building up the part concerned, so that there remains unappropriated a quantity of cells, it may be very few in number, which, owing to their embryonic character, are endowed with a marked capacity for proliferation. . . . The new born infant brings with it into the world, not the tumor, but merely the superabundant cell-material, and from the latter, if circumstances be favorable, a tumor may grow later on." (Cohnheim, "Lectures in General Pathology," Sydenham Soc. Publications, p. 760 *et seq.*) And it is further stated that in support of this view are to be regarded the congenital nature and early development of tumors; their atypical structure, their hereditary tendency, their occurrence in situations in which, during the development of the embryo, considerable complexity exists, and their frequent primary multiplicity.

It remains to indicate how these conditions are fulfilled by the case under consideration, and what further evidence of such an origin can be derived from observations of abnormalities in development affecting the regions in which the tumor was present.

Cohnheim (*idem.*, p. 762-763) states expressly that "the occurrence of the same kind of tumor in children of the same parents may point to hereditary influence, although it has not existed in the immediate progenitors," and in the history we have referred to three cases of eye tumor in the same family, all occurring between the fourth and sixth month, and hence of congenital or early acquired nature.

It is a mere supposition, it is true, that the tumors in all three cases were similar in structure to the one just described, and yet such an inference may not be entirely unwarranted. Of their malignancy there is evidence in the occurrence of metastases and death, and the ophthalmoscopic observations point to their retinal origin.

In all of the cases the tumors were multiple or early became so, and in this case, at least, both eyes were affected, although seemingly not at the same time. The atypical character of the tumor examined is striking, and admitting a histological resemblance to certain tissues of the normal retina, the morphological dissimilarity is evident and suggestive.

The complex nature and development of the retina, and the complicated series of changes in the vitreous humor and lens are to be regarded as especially predisposing to abnormalities in constitution. In the vitreous humor and lens there is a provisional set of blood vessels anastomosing with the vessels of the foetal retina. The provisional vessels should have disappeared at birth, but there are cases on record in which they or their germs have persisted. At times the arteria hyaloidea remains in a partly obliterated condition (Th. Leber, Stricker's "Manual of Histology," 1872, p. 861). Again, cells of an embryonic type have been described as present in the vitreous chamber and on the surface of the retina in post-foetal life (Balfour and Foster, "Elements of Embryology," 1883, p. 150; Kölliker, *idem.*, 1879, Vol. II, p. 666, and Iwanoff, *Archiv. f. Opth.*, Bd. XI, I, p. 155).

Finally, in the normal retina the blood vessels reach only as far forward as the external nuclear layer, but do not enter that layer. This leaves the two most external layers of the retina non-vascular. In our tumor the elements of these layers, while adjacent to blood-vessels are not, perhaps, in a more intimate relation with them than in the normal structure.

In conclusion I wish to express my indebtedness to Professor Welch and Dr. Councilman for their generous aid in describing this tumor.

EXPLANATION OF FIGURES.

FIG. 1. Diagrammatic representation of the retina showing origin of the tumor and section of the tumor at the retinal attachment. *A.* Ganglionic layer, layer of nerve fibres and internal limiting membrane of the retina. *B.* Internal molecular layer. *C.* Internal nuclear layer. *D.* External molecular layer. *E.* External nuclear layer. *F.* External limiting membrane and rod and cone layer. *a.* Areas of degenerated cells in the tumor at its attached border. *b.* Origin of the tumor in the external nuclear layer. This layer at the point of origin is noticed to be pushed upwards. The darker nuclei are the proper round cells of the tumor surrounding the peculiar rosettes.

FIG. 2. Representing the part of the tumor adjacent to the lens showing the processes of blood vessels and cells.

A. Process cut transversely. *a.* Blood vessel in the centre with the rosettes and round nuclei arranged around it. *B.* Process cut longitudinally showing the disposition of rosettes and round cells. *C.* Branching process. *D.* Areas of degenerated cells between the processes. Among the degenerated cells groups and single preserved round cells are to be seen. *E.* Masses of cells in a state of cell fusion.

FIG. 3. A rosette with its accompanying round cells highly magnified. The internal ring is made up of the delicate processes corresponding to the rods and cones; the middle ring represents the external limiting membrane. and the outer ring the nuclei of the rods and cones, and surrounding this are the so-called round cells of the tumor.
